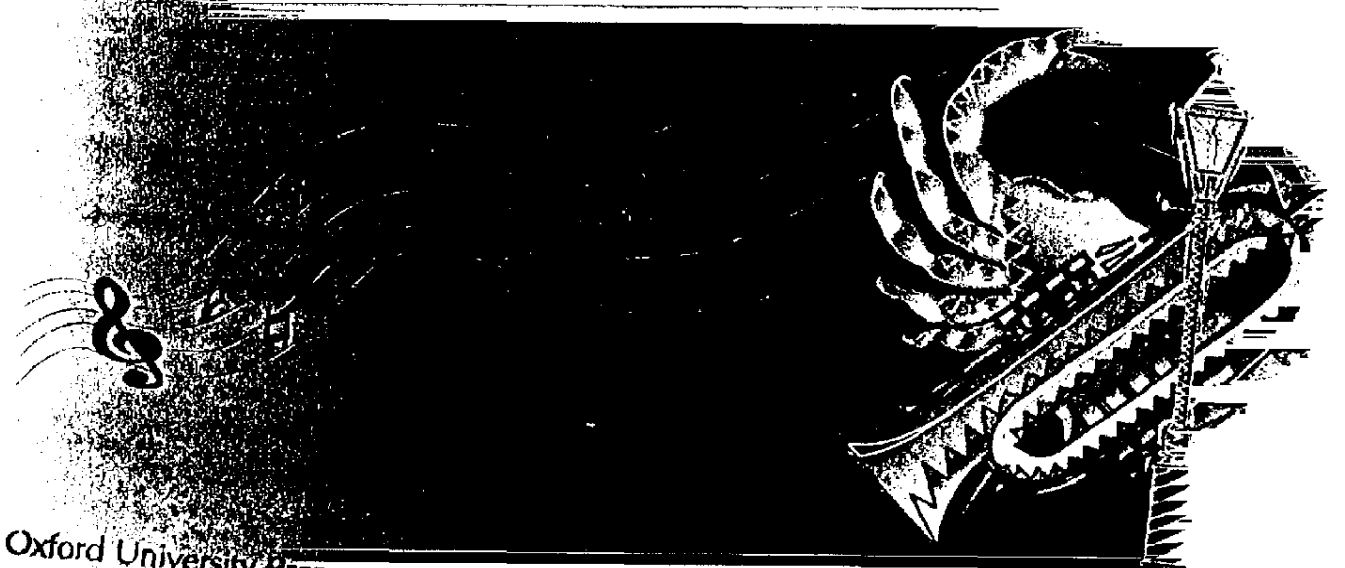
Supplement

ANNUAL MEETING

TOXICOLOGICAL SCIENCES

Formerly Fundamental and Applied Toxicology

The Toxicologist



Oxford University Press

Volume 48, Number 1-S, March 1999

The Toxicologist

An Official Publication of the Society of Toxicology

and

Abstract Issues of

TOXICOLOGICAL SCIENCES

An Official Journal of the Society of Toxicology
Published by Oxford University Press, Inc.

Abstracts of the
38th Annual Meeting
Volume 48, Number 1-S
March 1999

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshop, roundtable, and poster sessions of the 38th Annual Meeting of the Society of Toxicology, held at the Ernest N. Morial Convention Center, New Orleans, Louisiana, March 14-18, 1999.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 419.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 444.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1767 Business Center Drive, Suite 302
Reston, VA 20190-5332
http://www.toxicology.org

*untreated control groups. Measurement of liver T4-uridine diphosphate glu-*curonosyltransferase (UDP-GT) activity at week 4 revealed no significant intergroup differences. These results suggest that thyroid proliferative lesions were induced by KA administration due to continuous serum TSH stimulation through the negative feedback mechanism of the pituitary-thyroid axis, with decreases of T3 and T4 caused by a mechanism independent of T4-UDP-GT activity.

1107 COMPARATIVE 30-WEEK DERMAL TUMOR PROMOTION EVALUATION OF CIGARETTE SMOKE CONDENSATE FROM A REFERENCE CIGARETTE AND AN ECLIPSE PROTOTYPE (7026A) TEST CIGARETTE IN FEMALE SENCAR MICE.

D R Meckley[1], A T Mosberg[1], J D deBethizy[1], K R Van Kampen[2]. [1]*R J Reynolds Tobacco Co., Winston-Salem, NC;* [2]*The Van Kampen Group, Ogden, UT.*

A 30-week dermal tumor promotion assay was conducted to compare the potential dermal tumor promotion activity of mainstream cigarette smoke condensate (CSC) collected from an ECLIPSE prototype cigarette (7026A), which primarily heats tobacco, and a 1R4F (University of Kentucky) reference cigarette. Mainstream CSC's were collected by cold trap from smoke generators using the Federal Trade Commission puffing regimen. Female SENCAR mice were "initiated" with a single 75 ug application of DMBA to the shaved dorsal skin. The CSC's were then applied to the skin three times per week for 29 weeks. Each CSC was administered at 10, 20, or 40 mg tar/application to groups of 40 animals. End-points included body weights, clinical observations, organ weights, dermal tumor development data and histopathology. The numbers of dermal tumors and the numbers of dermal tumor-bearing animals for the 1R4F reference CSC were statistically different from the "DMBA-initiated" and "acetone-promoted" control groups, and increased with increasing exposure. The number of dermal tumor-bearing animals for the high-dose 7026A prototype CSC was statistically significantly different from the control groups. The numbers of dermal tumors for the mid- and high- dose 7026A prototype CSC were statistically different from the control groups and increased with increasing exposure. When corresponding dose levels of reference and 7026A CSC were compared to each other, the mid- and high-dose 7026A CSC groups had statistically fewer dermal tumors and tumor-bearing animals. In this assay, the dermal tumor-promotion potential of the 7026A CSC was, therefore, substantially reduced when compared to the 1R4F reference CSC.

1108 THE EFFECT OF CIGARETTE SMOKE ON THE METABOLISM OF THE TOBACCO-SPECIFIC NITROSAMINE 4-(METHYLNITROSAMINO)-1-(3-PYRIDYL)-1-BUTANONE (NNK) IN THE A/J MOUSE.

D J Doolittle[1], E Richter[2], A R Tricker[3], and B G Brown[1]. [1]*RJ Reynolds Tobacco Company, Winston-Salem, NC, USA;* [2]*University of Munich, Munich, Germany;* [3]*FTR, Neuchatel, Switzerland.*

The effect of short-term exposure to whole cigarette smoke on the metabolism of the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was studied in the A/J mouse. Mice (n=12) were exposed to either HEPA-filtered room air (control group) or 1R4F cigarette smoke for 2 hrs at a concentration of 0.6 mg particulate matter per liter of air. Immediately following nose-only inhalation, all animals received an intraperitoneal (i.p.) administration of 7.5 μmole/mouse of NNK containing 10 μCi of [^{3}H]NNK and then placed in metabolic cages for 24 hr urine collections. Collected urine was used to quantify the stable end products of the α -hydroxylation metabolic pathway, which activates NNK, and stable end products of NNK detoxification. The metabolites resulting from NNK activation by α -hydroxylation (hydroxy acid and keto acid) were significantly ($p<0.05$) reduced to 85% and 58% of control, respectively. Moreover, detoxification to the NNAL and NNAL-glucuronide metabolites increased significantly ($p<0.05$) to 108% and 116% of control, respectively. These results indicate that co-administration of cigarette smoke shifts the metabolism of NNK towards detoxification pathways compared to when NNK is administered alone. These results are consistent with previous studies demonstrating that cigarette smoke co-administration markedly reduces the formation of O^{6}MeG DNA adducts following NNK administration.

1109 TUMOR PROMOTING ACTIVITIES OF XYLAZINE (XZ) AND ITS METABOLITE, 2,6-DIMETHYLANILINE (DMA), IN A TWO-STAGE NASAL CARCINOGENICITY MODEL IN RATS INITIATED WITH N-BIS(2-HYDROXYPROPYL)NITROSAMINE (DHPN).

T Koujitani[1], K Mitsumori[1], K Yasuhara[1], H Kobayashi[2], H Onodera[1], H Takagi[1], and M Hirose[1]. [1]*Division of Pathology, National Institute of Health Sciences, Tokyo, Japan;* [2]*Chemistry Division, Institute of Environmental Toxicology, Ibaraki, Japan.* Sponsor: T Shirai.

XZ is an α_2-adrenergic agonist that is used in food-producing animals as a sedative agent. It has been reported that DMA, a metabolite of XZ, induced nasal cavity tumors in rat 2-year carcinogenicity study, but a carcinogenicity study of XZ has not been performed. To examine the tumor promoting effects of these chemicals, five-week old F344 male rats were given a single subcutaneous injection of DHPN (2400 mg/kg). Starting one week after the injection, the animals were given diet containing DMA (3000 ppm), XZ (1000 ppm, a maximum tolerated dose), or basal diet for 52 weeks. Histopathologically, the total incidences of the nasal tumors including papillomas, adenomas or carcinomas in the DMA, XZ and basal diet groups were 16/30 ($p<0.01$), 6/20 and 4/20, respectively. Dysplastic cell foci in the DMA, XZ and basal diet groups were observed at the incidences of 10/30 ($p<0.01$), 2/20 and 1/20, respectively. In the second experiment, rats were given diet containing DMA (3000 ppm) or XZ (1000 ppm) for 28 days, and plasma levels of DMA and/or XZ were measured. Plasma levels of DMA in the DMA group at days 7 and 28 were 0.36 and 0.20 μg/ml, respectively, but those of DMA and XZ in the XZ group were below the detection limit (0.02 μg/ml). These results strongly indicate that DMA has a tumor promoting effect in the rat nasal cavity, and suggest that XZ is not carcinogenic to the rat nasal cavity, because the amounts of XZ and DMA in plasma were too small to exert promotion activity in the XZ group.

1110 MIREX SKIN TUMOR PROMOTION IN MALE MICE IS REGULATED BY ESTRADIOL.

K L Porter, C L Robinette and R C Smart. *Dept. of Toxicology, North Carolina State University, Raleigh, NC, USA.*

Mirex, an organochlorine pesticide, is a potent tumor promoter in female mouse skin. Previous studies in our laboratory have shown that intact female mice are 3 to 4 times more sensitive to mirex promotion than ovariectomized (OVX) female mice, and that 17β -estradiol (E2) implants in OVX female mice can partially restore the intact female response. In addition, female mice are 3 to 4 times more sensitive to mirex promotion than male mice, further supporting a role for E2 in mirex promotion. Since male mice are relatively resistant to mirex promotion, we wanted to determine if chronic systemic E2 elevation could increase the mirex tumor response of male mice to that of females. Intact male mice were initiated with 7,12-dimethylbenz[*a*]anthracene and two weeks later were divided into groups and subjected to the following treatments; castration and blank implants, castration and E2 implants or sham castration and blank implants. Castrated male mice developed 3 fold fewer tumors than intact mice, and E2 implants were able to completely reverse the effects of castration on mirex promotion, but could not increase the male tumor response to that of intact female mice. We found that serum E2 in castrated male mice with E2 implants was 15.5 ± 5.7 pg/ml, which is at the low end of the intact cycling female range of 5.8 to 79.6 pg/ml. This difference could account for the inability of male mice to acquire the female mirex tumor response. Surprisingly, the serum E2 levels in intact and castrated male mice with blank implants were 10.1 ± 3.6 pg/ml and 9.1 ± 3.1 pg/ml, respectively. To address the disparity between serum E2 levels and mirex promotion sensitivity in intact and castrate mice, we assayed E2 in skin and found that skin E2 levels are at least ten times greater than serum E2 levels in intact male mice, and we are currently examining skin E2 levels in castrate mice. These data suggest that E2 is important in regulating mirex promotion in male mice and that cutaneous E2 levels and factors regulating E2 levels and/or responsiveness are as important as systemic serum E2. (NEIHS Grant ES08127)